Metformin-induced Lactic Acidosis Associated with Multiorganic Failure

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Lactic acidosis is a rare but severe complication in patients with type 2 diabetes treated with metformin. Patients with lactic acidosis show commonly signs of shock, tissue hypoxia, acute hepatic or renal failure and the link between metformin therapy and lactic acidosis may be coincidental, associated or causal. Excessive plasma metformin concentrations show that lactic acidosis is due to a toxicological mechanism. We report a case of severe multiorganic failure in a subject after treatment with high doses of metformin.

Key words: Metformin, Lactic acidosis, Multiorganic failure, Tissue hypoxia

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1. INTRODUCTION

Lactic acidosis is a rare but severe complication in patients with type 2 diabetes treated with metformin (1, 2, 3). Patients with lactic acidosis show commonly signs of shock, tissue hypoxia, acute hepatic or renal failure and the link between metformin therapy and lactic acidosis may be coincidental, associated or causal (4). Excessive plasma metformin concentrations show that lactic acidosis is due to a toxicological mechanism (5). We report a case of severe multiorganic failure in a subject after treatment with high doses of metformin.

2. CASE REPORT

A 42 years old female was admitted in our service of nephrology for oliguria, arterial hypertension 200/110 mmHg, tachycardia (cardiac frequency 115/min), and dyspnea and chest pain. Two weeks ago the patient was diagnosed for diabetes mellitus (DM) type 2 and hypertension, and had started the treatment with metformin 3 g/day, bisoprolol 6.5 mg/day. Three days later, she started vomiting and after oliguria displayed. In her life history the patient had cholecystectomy few years ago. The admission examinations resulted: blood urea: 107 mg/dl; creatinine: 11 mg/dl, sodium: 118 mEq/l, potassium: 5.4 mEq/l, chloride 105 mEq/l, glucose: 226 mg/dl, SGPT 24 UI/l, SGOT 17 UI/l; complete blood count showed: red blood cells: 4.200.000 /mm³, white blood cells: 7200 /mm³, hemoglobin: 12.3 g/dl, erythrosedimentation: 22 mm/hour; arterial blood gas showed: red blood cells: 4.200.000 /mm³, white blood cells: 7200 /mm³, hemoglobin: 12.3 g/dl, erythrosedimentation: 22 mm/hour; arterial blood gas showed severe lactic acidosis: pH: 7.1, EU: -18, lactates 8 mmol/l, bicarbonates 7 mEq/l. Chest X-ray was normal. Serum toxicological results, namely benzodiazepines, tricyclic antidepressants, opiates and barbiturates were negative. Cardiac problems were excluded after electrocardiogram, echocardiography and cardiologist consult. We started stimulation for diuresis with dopamine and furosemide. Dyspnea persisted and she required oxygen-therapy all the time. There was a wide fluctuation in the blood pressure values till hypotension 50/20 mmHg was established, associated with sopor and loss of vision. The treatment consisted in prednisolone and adrenaline given with perfusion. After these procedures the values of blood pressure raised 120-140/80-90 mmHg. Because of situation’s deterioration, the patient was transferred to the Intensive Care Unit for further treatment. The endotracheal intubation and mechanical ventilation were performed. The patient’s condition continued to be serious, with sopor and then she fell to 3-points coma (Glasgow Coma Scale score). She continued with oligoanuria (350-450 cc in 24 hours) despite the doses of diuretics. Blood pressure was held only through vasoconstrictor drugs. The next biochemical results revealed: blood urea: 166 mg/dl, creatinine: 15 mg/dl, glycemia: 303 mg/dl, sodium: 108 mmol/l after 127 mmol/l, potassium: 4.8 mmol/l, chloride: 76 mmol/l, SGPT: 485 UI/l, SGOT: 1484 U/I, amylase: 1484 U/I; blood gases: pH: 6.87, BE: -28, HCO₃⁻: 3 mEq/l, PCO₂ mmHg: 24; central venous pressure (CVP): 24 mm H₂O.

The ultrasound of the abdomen was normal. The therapy consisted in dobutrex, furosemide, cephruxomine, sodium bicarbonate, and prednisolone. The situation was complicated with cardiac failure and cardiovascular collapse, with a severe hypotension (blood pressure 40/20 mmHg). The patient
dies one day after treatment in intensive care unit.

Patient’s disease history (diabetes mellitus type 2 for whom treatment with metformin was initiated 3g/day), its clinical data (acute renal failure, acute respiratory insufficiency, cardiaic insufficiency and metabolic acidosis), laboratory examinations, suggest us for a case with lactic acidosis from metformin associated with multiorganic failure.

3. DISCUSSION

Lactic acidosis results when blood pH is lower than 7.25 and lactates in blood are higher than 5 mmol/l. Hyperlactatemia is defined when lactates in blood are in ranges between 2-5 mmol/l (1). Two types of lactic acidosis are recognized:
- Type A, triggered by hypoxia, which may result from tissue hypoperfusion in cases of left ventricle failure, reduced cardiac debit, or reduced arterial oxygenation -asphyxia, hypoxemia, carbon monoxide poisoning, severe anemia (2, 3, 4);
- Type B, which is classified into three groups:
  - Type B 1, in septic states, in acute renal failure, hepatic disease, diabetes mellitus, neoplasms, malaria, cholera;
  - Type B 2, resulting from drug toxicity (biguanides-metformin, fenformin and others like paracetamol, aspirin, negram, isoniazide, sodium nitroprusside, catecolamines, etc.);
  - Type B 3, as a result of increased physical activity, grand-mal, etc.

Lactic acidosis from metformin is a rare condition, occurring 1: 30.000 patients. It is associated with a high mortality up to 50% (2, 3). Since lactates are eliminated with hepatic and renal route, lactic acidosis occurs in those persons who have had previous hepatic, renal, or cardiac failure or dehydration state. There are described fatal cases of lactic acidosis from metformin in the literature (4, 5), complicated by respiratory insufficiency, sometimes associated with irreversible tubular necrosis.

Abnormal hyperlactatemia results from an exaggerated transformation of piruvates into lactates. Lactic acidosis resulting from increased blood lactates occurs when the capacity of the buffer systems of the body is exceeded. This occurs in states of tissue hypoxia (1, 3).

The beginning of acidosis can be very rapid, within minutes, or may develop for a few days with weakness, abdominal discomfort, vomiting, cardiac arrhythmias, muscle pain, signs of shock such as cyanosis, cold extremities, hypotension, dyspnea, stupor or coma, acute hepatic or renal failure. Therapy consists in the supportive care, disease management, reduction and correction of acidemia, acceleration of lactate metabolism and elimination of drug through kidney or dialysis (6). The patient should be well ventilated, should be given abundant amount of liquids, antibiotics, sodium bicarbonate (7, 8, 9).

There is controversy regarding its use, and in general it should be avoided. The sodium bicarbonate perfusion results in carbon dioxide production, which leads to intracellular acidosis. Prospective studies on the use of sodium bicarbonate on lactic acidosis have not shown beneficial effects in terms of improvement of acidosis. Continuous veno-venous hemodiafiltration is another alternative of treatment in severe renal failure (10, 11). It is seen that bicarbonate hemodialysis is the best option. Dicloracetate is the most potent stimulator of pyruvate dehydrogenase, inhibiting the glycolysis process. It has also an inotropic positive effect (12).

Other therapies may include: combination of glucose with insulin, thiamine 100 mg i.v. and then 50 mg/day orally for 1-2 weeks, sodium nitroprusside.

The very rapid progression of multi-organic failure in our patient, comatose status for which she was intubated and the severe heart failure with underlying cardiovascular collapse, did not allow us to put her on hemodialysis.

4. WHAT CAN WE LEARN FROM THIS CASE?

In a patient with type 2 diabetes mellitus before starting treatment with oral hypoglycemiant (metformin) should first be sure that patient is free from hepatic injury, previous renal failure, and that there are no contraindications. Their dose should be optimal (daily dose metformin alone should not be greater than 2.5 gram and should also vary depending on patient age) because overdose can be associated with symptoms of lactic acidosis and other complications with fatal consequences for life.

REFERENCES